UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/187,879	01/27/1994	HARRIET L. ROBINSON	UMMC9103A2	5747

21005 7590 04/01/2002

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	49

DATE MAILED: 04/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 48

Application Number: 08/187,879
Filing Date: January 27, 1994
Appellant(s): Robinson *et al.*

Elizabeth W. Mata
For Appellant

SUPPLEMENTAL EXAMINER'S ANSWER

This is in response to Appellant's Reply Brief on appeal filed August 7, 2001.

The reply brief has been considered by the examiner but is not found persuasive for the patentability of the full breadth of the claimed methods which embrace any route of administration of any antigen encoding DNA so as to provide protection against any SIV or HIV infection, wherein said protection as contemplated by Appellant in the as-filed specification (page 7, lines 9-11) includes full protection against any SIV or HIV infection and/or partial protection against the infection (protection against a SIV or HIV infection to a lesser extent that would occur without immunization, as indicated on page 7 of the as-filed specification and on page 4, last paragraph of the reply brief).

The rely brief is not found persuasive because of the reasons set forth in the examiner's answer dated June 4, 2001 and because of the following reasons:

Status of Claims (page 1 through page 2 of the Reply Brief)

The appellant's statement (pages 1 and 3 of the reply brief) of the status of claims as set forth in the brief and the examiner's answer is noted and accurate.

Issues (pages 2 through 3 of the Reply Brief)

The appellant's statement (pages 3 and 4 of the reply brief) of the issues as set forth in the brief and the examiner's answer is noted and accurate.

Response to the Discussion of the Reply Brief (pages 3 through 12 of the Reply Brief)

In order to determine whether or not undue experimentation is required to practice the full breadth of the claimed SIV or HIV immunization methods at the time the invention was made, the Office had relied on the *Wands* factors: the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation necessary.

The Office's position is that nearly all of the Wands factors weigh against enablement in this application:

Breadth of claims and Nature of Invention

The examiner takes the position that the claimed invention is an immunization method of using any DNA construct encoding any HIV or SIV antigen so as to provide a partial and/or full protection in a mammal against a real world infection by any SIV or HIV virus. It is apparent from the brief, the examiner's answer dated June 4, 2001, and the reply brief, that the examiner 's position as to the nature of the invention was not disputed or challenged by Appellants. While Appellant's interpretation (the reply brief, pages 3-4, particularly last paragraph of page 4) of the intended breadth of the claimed

immunization methods with respect to the "immunizing" on the basis of Appellant's disclosure is correct, the breadth of the DNA immunization methods against any SIV or HIV infection is not commensurate with the scope of enablement provided by the specification at the time invention was made (1992).

In addition, the Office does not dispute the fact that DNA transcription units can be constructed by routinely employed recombinant DNA techniques at the time the invention was made (the reply brief, page 4, last paragraph), however, the issue is whether or not an DNA immunization method of using any DNA transcription unit encoding any SIV or HIV antigen can be practiced by a skilled artisan to partially and/or fully protect a mammal against SIV or HIV infection without undue experimentation, particularly on the basis of Appellant's disclosure and the state of the prior art at the time this as-filed application was filed (1994) and claims for priority (1992).

Amount of Direction Provided by the Inventor, State of the prior art, Working Examples, and Quality of Experimentation Needed Based on the Disclosure

The reply Brief (page 5) mainly reiterates that the guidance with respect to the making and use (routes of administration) of SIV or HIV antigen encoding DNA constructs is sufficiently described by the as-filed specification, and that on the basis of Appellant's guidance, Working examples and the Robinson Declaration (submitted March 1, 1996, the contents of which are essentially the same as that

disclosed in the Lu *et al.* reference, published 1996, cited by Appellants in the reply brief), a skilled artisan would have been able to determine, without undue experimentation, as to which of the DNA constructs embraced by the full breadth of the claimed methods would exhibit an intended immunization effect, and to practice the full breadth of the claimed method without any undue experimentation. While the Office does not dispute the fact that guidance with respect to the preparation of DNA constructed that can be used subsequently for further experimentation on the DNA immunization methods was sufficiently described by the as-filed specification, the issue is whether or not a skilled artisan would have been able to, without any undue experimentation, immunize a mammal at risk of having a real world or natural SIV or HIV infection (primates and humans), with any of the disclosed DNA constructs including those employed in the working examples and the Declarations of record for any of the intended effects as contemplated by Appellants at the time the invention was made, *e.g.*, conferring a partial and/or full protection against a specifically named SIV or HIV infection, let alone the full breadth of DNA vaccine constructs encoding any SIV or HIV antigen so as to trigger an immunoprotective response against any HIV or SIV infection in a host vaccinated.

With respect to the state of the prior art, no prior art from the time the invention was made until now has demonstrated that the immunization method as claimed has been employed in any mammal having or at risk of a natural SIV or HIV infection, whereby a partial or protection of the infection can be established or exhibited against the SIV or HIV infection. The Office then reasonably had concluded that, on the basis of the evidentiary support disclosed in

the prior art of record, DNA immunization against a naturally occurring HIV or SIV infection in a mammal (primates such as monkeys and humans) in 1992-1/1994 is not an established but rather an emerging technology that was still undergoing research for an art-recognized model and/or efficacy of any protection, *e.g.*, see Hayes (page 1280, 1993), Hoffenbach *et al.* (page 142, 1989), Butini *et al.* (abstract, 1994), Glasser (1996), Rekosh *et al.* (page 334, 1988), Weiss (page A2, 1997), Cohen and Fauci (page 88, 1998), Kuby (1992), Gilboa and Smith (1994, page 141 through page 142), and Johnson (page 58, 1992).

With respect to the amount of direction or guidance present and the presence of working examples and in order to rebut the Office position as to the doubts expressed in the art of record and the subsequent lack of reasonable predictability to carry out the claimed invention with the intended utility, Appellants, in both the brief and reply brief, had relied on Example 14, the Robinson Declaration (the "Data Declaration," submitted on March 1, 1996), and the Lu *et al.* reference (1996).

Response:

Section 112, Paragraph 1, provides, in relevant part that "[t]he specification shall contain a written description of the invention, and the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. . . . "

The issue is not whether any plasmid vector expressing any SIV or HIV antigen can be made by simple and routine DNA recombinant techniques, but rather whether one skilled in the art would have been able to employ the constructed plasmid vectors as DNA vaccines for the only intended use of generating any and/or all protective responses in any and/or all infectious mammals including humans, without any undue experimentation, particularly on the basis of applicant's disclosure and the doubts expressed by the art of record. For the claimed invention to be enabling under 35 U.S.C. 112, first paragraph, the specification of the as filed application must teach one skilled in the art how to make and use the full scope of the claimed invention "without undue experimentation", and the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to one skilled in the art.

More specifically as to Appellant's reliance of Example 14 and the Robinson Declaration to assert that the currently pending claimed DNA vaccine method is enabling in its full breadth under 35 USC 112, first paragraph, examples 11 –15 of the specification describe making and administering DNA vectors encoding antigens of SIV and HIV, but Appellants have not provided any guidance and/or factual evidence showing a reasonable extrapolation from the disclosure to any DNA vaccine/immunization effect.

The only evidence that is relevant to the claimed invention is the Robinson Declaration (paper No: 15). The Robinson Declaration teaches that multiple administrations, *e.g.,* gene gun, intramuscular, and intravenous administration, of a mixture of specifically constructed plasmids

encoding at least a SIV env antigen (extracellular domain and/or the receptor binding subunit of a SIV envelope protein) to macaques caused viral loads to be reduced to chronic levels more rapidly than occurs in control animals, but neither the application nor any of the Declarations of record nor any prior art of record nor any art of record even five years after the effective filing date of the application has shown by clear and convincing evidence that by using any route of administration of any SIV or HIV antigen expressing plasmid vector, an immunoprotective response can be reasonably generated in any mammal at risk of being infected by a naturally occurring SIV or HIV strain. Even in the Robinson Declaration (paper No. 15), the macaque model fails to protect the immunized animal against SIV infection or death by AIDS (caused by any HIV strain infection). The breadth of the claimed invention when interpreted in light of the as-filed specification clearly intends to embrace the utility of conferring a protection (partial and/or full protection) against an infectious SIV or HIV infection in any mammal, *e.g.*, primate and humans. The issue is then would a skilled artisan have recognized that a rapid reduction of viral loads to chronic levels in the macaque model relative to the control animals represent applicant's utility to confer any and/or all intended protection in primates and/or humans against HIV or SIV infection. In light of the fact that DNA vaccine against HIV or SIV in primates or human has not been conducted or established in the prior art of record, the examiner then turns to the state of prior art for guidance in making the determination whether or not a reasonable nexus between applicant's macaque model and the intended utility of Appellant's claimed invention

can be established.

The state of the art at the time , and even after the application was filed, is well-documented. Haynes (Science, Vol. 260, pp. 1279-1286,) stated in 1993 :

> "In spite of an extraordinary amount of work in search of an animal model for human AIDS, no animal model exactly mirrors human HIV infection. In general, current animal models of HIV or simian immunodeficiency virus (SIV) infection either do not develop AIDS symptoms, do not develop immune responses analogous to human anti-HIV T and B cell response, or involve the use of endangered species such as chimpanzees. Thus, many important scientific questions of HIV vaccine development must be answered in human clinical trails" (page 1280, first column).

As recently as 1996, Glasser (Genetic Engineering News, Biotech Firms Shifts Focus Toward Therapeutic HIV vaccine Development, 1996) reviewed the state of the art of DNA HIV vaccine and concluded:

> "Many obstacles that have thwarted HIV vaccine development in the past continue to challenge researchers and clinicians. These obstacles are :
> - The need to induce humoral (antibody), cellular (cytotoxic T lymphocyte-mediated), and mucosal (preventing viral entry at mucosal surfaces) immunity.
> - HIV resides in immunoprivileged sites and can remain latent for years. HIV causes immunosuppression, further hindering the body's ability to contain the virus and prevent opportunistic infections.
> - How the virus destroys immune cells is not fully understood.
> - No good animal model exists.
> - HIV continuously mutates: different strains are prevalent in various parts of the world; field isolates often differ from the laboratory strains used to develop vaccines; and after infection, HIV can mutate within the host, and an infected person can harbor multiple forms of the virus.
> - The appropriate clinical end points for evaluating therapeutic vaccines are not clear".

A number of skilled artisans commented on a study of DNA vaccines in chimps, as

reported in the Washington Post, Genetic Vaccine Keeps Chimps Protected Against AIDS Virus, page A2, 4/30/1997 (Weiss):

> "Genetic vaccination is one of several approaches under investigation in what has remained a mostly disappointing effort to develop an AIDS vaccine. Success has been hampered by HIV's great variability, which makes it a moving target for vaccine developers, and by the lack of a good animal model for testing candidate vaccines",
>
> "Equally frustrating, scientists still don't know what, precisely, an AIDS vaccine ought to do in the body to be effective. Neither of the immune system's two armies for fending off microbial invaders-antibodies and killers T cells- reliably win the battle against HIV. Vaccines seek to boost the strength of one or both of those immune system armies, but no one knows which is more important",
>
> "Marc Girard, chief of molecular virology at the Pasteur Institute near Paris, was among several who criticized use of the SF2 strain to test AIDS vaccines. 'The challenge they used is not a strong challenge,' he said. 'It 's a wimpy virus and this vaccine may not be strong enough for a more virulent strain"; and

Even in 1998, Cohen and Fauci (JAMA, Vol. 280, No. 1: 87-88) indicated:

> "the development of a safe and effective vaccine continues to encounter a host of sobering challenges, including geographic variability of HIV subtypes, and the lack of correlates of protective immunity in HIV infection"(page 88, column 1).

In 1992, about the time the original parent of the instant application was filed, Kuby observed (Immunology, W.H., Freeman & Co. New York):

> "Unfortunately the presence of high titers of circulating antibody to HIV proteins in no way indicates protective immunity", that "the antibody has so little effect seems to be frequent antigenic drift in HIV", that "some studies have indicated that anti-HIV antibody-HIV immune complexes to Fc receptors on macrophages and subsequent receptor medicated endocytosis may lead to increased HIV infection of macrophages", and that "several observations indicate that immune regulation is disturbed in AIDS patients, although the mechanisms underlying these disturbances are not entirely clear".

The evidence found in the art from 1992 through 1998 clearly demonstrates there was no good animal model to test the efficacy of DNA immunization against HIV or SIV infection in primates or humans. At best, the macaque model, in which a simple reduction of viral loads was shown within a statistically insignificant 6 weeks post challenge is *an art recognized model for studying and investigating the mechanism of pathogenesis of SIV infection.* It does not lend clear evidentiary support for a skilled artisan to reasonably extrapolate to partial or full protection against any HIV or SIV infection in primates or humans. In fact, the Robinson Declaration is indicia of the lack of reasonable predictability of the claimed subject matter, *e.g.,* SIV or HIV DNA vaccine. While the cited references state that that cellular immune responses, *e.g.,* cytotoxic lymphocyte or CD4+ production, are essential for the fight against development of AIDS, the Robinson Declaration (Paper No. 15) states that "consistent with failure to achieve long-term reductions in viral loads, all of the vaccine animals exhibited steadily declining CD4+ cells", that "the trial was terminated at one year post-challenge", that "at this time, the three macaques in the gene-gun only group, and one of the two control macaques (the one with the steady CD4+ level), had succumbed to AIDS (figure 8), and that "the second control monkey and the four monkeys in the multiple route group did not have clinical signs of AIDS at the time of euthanasia". Applicants' results, where immunized macaques in the gene-gun only group failed to exhibit any protective response against SIV infection, support the conclusion that the full

scope of the claimed invention, encompassing any DNA vaccine regardless of what SIV antigen expressing plasmids and/or routes of administrations are employed in any primate or human infected by any SIV or HIV, or in any primate or human at risk of being infected by SIV or HIV, is not enabled.

Other than the fact that the specification provides the most general guidance as to how the claimed method can be practiced, Appellant relies on the working examples and the Robinson Declaration. However, neither the working examples nor the Robinson Declaration significantly reduce the amount of undue experimentation needed to practice the claimed method, for a number of reasons. First and as stated in the art of record, HIV and/or SIV viruses are a very diverse and genetically complex group of viruses that do mutate and develop into distinct strains having distinct antigenicity. Neither Appellant's response nor any of the submitted Declarations addresses this obstacle other than asserting an opinion that their only working example, demonstrating a "reduction of viral load" at 4 or 6 weeks post-challenge against the uncloned SIV mac251 virus, provides a reasonable expectation that any DNA vaccine encoding any SIV or HIV antigen can be used to generate at least a partially immunoprotective response against any and/or all SIV or HIV strains in a vaccinated host. Second, in the Macaque model as shown in the Robinson Declaration (paper No. 15), though the four monkeys in the multiple route did not have clinical signs of AIDS at the time of euthanasia, neither did not one of the two control monkeys. Furthermore, the trial was terminated at one year post-challenge. The time for the

AIDS progression can be much longer than one year. The challenge virus was an uncloned SIV mac251 virus. Johnson *et al.*, Intern. Rev. Immunol. Vol. 8, pp. 55-63, 1992, state that it typically takes longer than one year for AIDS progression where the virus is other than a 239 (the explanation for Table 1 appearing on page 58). Neither the reply brief nor any of Appellant 's responses addresses the specific concern set forth by the Office as to the lack of reasonable correlation between the "reduction of viral load" at 4 weeks post-challenge against the uncloned SIV mac251 virus and an immunoprotective response in a host vaccinated by any of Appellant's claimed DNA vaccine against any real world infection of SIV or HIV. Third, on the basis of the totality of the art of record, the exemplified Macaque model using multiple administrations comprising at least a gene gun administration of particularly named plasmid DNA, is not an art recognized model for predicting that partial protection can be produced using any DNA transcription unit encoding any SIV or HIV antigen in any primate or human infected by any SIV or HIV, or in any primate or human at risk of being infected by SIV or HIV, let alone the full protection against any SIV or HIV strain as embraced by the full breadth of the DNA immunization methods as claimed. Fourth, it is well accepted within the scientific community that induction of humoral (antibody), cellular (cytotoxic T lymphocyte-mediated), and/or mucosal (preventing viral entry at mucosal surfaces) immunity is essential to provide at least an immunoprotective response against SIV or HIV infection in primates and humans. However, neither the Robinson declaration nor the Lu *et al.* reference (1996) provides any factual evidence

to demonstrate such immunity. On the contrary, the Robinson Declaration (Paper No. 15) states that "consistent with failure to achieve long-term reductions in viral loads, all of the vaccine animals exhibited steadily declining CD4+ cells", ~~that~~ that "the trial was terminated at one year post-challenge", and "at this time, the three macaques in the gene-gun only group, and one of the two control macaques (the one with the steady CD4+ level), had succumbed to AIDS (figure 8), and that "the second control monkey and the four monkeys in the multiple route group did not have clinical signs of AIDS at the time of euthanasia". Apparently, this single working example relied upon by Appellant throughout the prosecution history, does not clearly demonstrate and thus does not enable any immunoprotective response against the laboratory uncloned SIV mac251 virus, let alone any immunoprotective response against any virulent strain of SIV or HIV that may have or would have infected primates and humans in the real world, particularly since a skilled artisan at the time the invention was made and even now would not have recognized that Appellant's conclusory statement, that regardless of the lack of humoral or cellular mediated immune response in a vaccinated host, a "reduction of viral load" during a statistically insignificant time period (6 weeks post-challenge) is the same or represents any immunoprotective response against any SIV or HIV infection in primates and/or humans. Neither Appellant nor any art of record established that a "reduction of viral load" at 6 weeks post-challenge, as shown in the Robinson declaration, would have been an immunoprotective one, or moreover, that one skilled in the art would have expected such a correlation in

1992-1/1994 or even now.

In the reply brief (pages 10-12), Appellant's doubts as to the reliance of the office on the Hoffenbach and Butini references have been considered fully the examiner but is not found persuasive for the reasons set forth in the immediately preceding paragraphs, Appellants have further asserted in the reply brief (pages 10-12):

1)

that Hoffenbach and Butini *et al.* (relied upon by the Office) do not accurately reflect the doubts as to the predictability and a protective response in primates and/or humans infected by SIV or HIV because both Hoffenbach and Butini *et al.* utilize "very small sample, drawing into question whether any conclusion can be drawn from these references concerning the relationship between CTL response to HIV and progression of disease and even whether they can be considered representative of the state of the art concerning relationships between CTL response and protection against the disease";

Response:

Appellant's statement as to the doubts regarding the credibility of both the Hoffenbach and Butini *et al.* references is an expressed opinion without any factual evidence to support that the Office erred in concluding that the prior art of record suggests that the science of making and using DNA vaccines against any SIV or HIV infection in primates or human was and still remains in its infancy. The references noted above (pp. 9-11) further support the examiner's

position.

2/

Appellants further asserted on page 10 of the response that cytotoxic T lymphocytes (CTL) are not always a necessary component to have a protective effect, and that "it has been demonstrated that even DNA vaccinations which raise low to undetectable titers of antibody can confer protection against disease (see, e.g., the Specification at page 30 *et seq.*)", thereby implying that any disclosed DNA vaccine as embraced by the claimed invention would confer a protective response against HIV or SIV infection in primates or humans, even if CTL response, and/or titers of antibody [against the antigen expressed by the DNA vaccine] is not detectable. In addition and as the evidentiary support for the position, Appellants state that their working examples [the SIVmac251 macaque model] is an illustration of successful protection against manifestations of disease (page 10 of the reply brief), and that a rapid reduction in viral load, such that described in the Data Declaration would still be possible, thus allowing generation of an immune response that lessens manifestation of disease and demonstrating "immunizing" or "partial protection" as the term is described in the specification. Furthermore and notwithstanding the clear and convincing evidence shown in the art of record employed by the Office, *e.g.,* Hayes (page 1280, 1993), Hoffenbach *et al.* (page 142, 1989), Butini *et al.* (abstract, 1994), Glasser (1996), Rekosh *et al.* (page 334, 1988), Weiss (page A2, 1997), Cohen and Fauci

(page 88, 1998), Kuby (1992), Gilboa and Smith (1994, page 141 through page 142), and Johnson (page 58, 1992), Appellants assert that since Appellants have, for the first time, demonstrated that immunization of a mammal [the SIVmac251 macaque model] by administering to the mammal [multiple administrations including at least a gene gun administration of the plasmid vectors as indicated on page 8 of the Examiner's Answer dated June 4, 2001] a DNA transcription unit comprising a DNA encoding an antigen of SIV, whereby the mammal was protected at least partially from the manifestation of disease caused by the SIV, is indeed possible.

Response:

In the present case, the examiner sets forth a reasonable basis for finding that the scope of the appealed claims is not enabled by the general description and the single working example shown in the Robinson Declaration (the SIV model). It is the examiner's position that Appellants have failed to meet this burden. The Office did not err in relying on the state of the art of record as a whole to reasonably conclude that an induction of any humoral and/or cellular mediated immune response and their subsequent immunoprotective response against any SIV or HIV infection in a vaccinated host by using SIV or HIV DNA vaccine is crucial for a likelihood of an establishment of a protective response. As discussed throughout the examiner's answer and in the immediately preceding paragraphs, in the absence of clear and convincing evidence

showing that a "reduction of viral load" at 6 weeks post-challenge, as shown in the Robinson declaration, would have been an immunoprotective one, or moreover, that one skilled in the art would have expected such an extrapolation in 1992-1/1994 or even now, the totality of the art of record adequately supports the Examiner's position that, in 1992, the physiological activity of SIV or HIV viruses was varied, complex, and that DNA SIV/HIV vaccines were and still are reasonably unpredictable, and thus, the only relevant working example as shown in the Robinson Declaration, as relied upon by Appellants in the brief and reply brief, would not have led one of ordinary skill in the art to believe reasonably that any primate or human at risk of being infected by any naturally occurring SIV or HIV virus strain, which often are virulent strains, could be immunized against infection by a simple administration of any DNA transcription unit encoding any SIV or HIV antigen.

Technology of using DNA vaccine to confer a protection by using any route of administration is routine

In addition and with respect more specifically to Appellant's belief that DNA vaccine by using any route of administration is reasonably predictive at the time the invention was made (1991-1994), Appellant had relied on the Pardoll an Beckereig reference (1995, page 167), which indicates that "injection of naked DNA through any of a number or routes reproducibly induces both humoral and cellular immune responses against the encoded antigen", to assert that DNA vaccine by administering any SIV or HIV encoded DNA (which is not necessarily limited to

naked DNA and/or a particular antigen encoded DNA) by any route of administration so as to provide a partial or full protection against HIV or SIV in primates or humans is reasonably predictive at the time the invention was made (1992 as being the earliest priority claim date, and 1/1994 as being the filing date of the as-filed application).

Response:

Appellant's argument has been considered but is not found persuasive because a well-established showing of an induction of a general immune response in animal models, *e.g.,* murine or rat models, wherein injection of "naked plasmid DNA" through a number of routes in the animal models without any clear and convincing evidence showing that a specifically induced immunoprotective response against any SIV or HIV infection can be established in vaccinated primate or human at risk of being infected by SIV or HIV, is not substantially sufficient to overcome numerous references that were cited in previous Office actions and this examiner's answer that clearly identify a number of difficulties and/or obstacles that a skilled artisan must overcome in the art of SIV or HIV DNA vaccines, which vaccines and their intended protective effects are fully embraced by the appealed claims. Furthermore, the fact that vaccines using live attenuated viral or recombinant protein had been established in the prior art of record (see Pardoll and Beckereig, page 167, column 2, last paragraph) does not lend any evidentiary support that Appellants' claimed DNA vaccines against any naturally occurring HIV or SIV infection in

primates or humans has been established. On the contrary, the art of record clearly indicates that no such vaccines, let alone DNA vaccines, have been shown to be effective in providing any immunoprotective response against any SIV or HIV infection in a vaccinated primate or human. In addition, one of the consistently held views within the scientific community as disclosed by the art of record clearly indicates that a sufficient induction of CTL response (cellular mediated immune responses) for generating a cross- immunoprotective response against any HIV strain is essential in the art of establishing an SIV or HIV DNA vaccine as humoral responses against an SIV or HIV encoded antigen are strain specific and poorly cross protective, particularly since HIV or SIV antigens (glycoproteins, for example) vary significantly among different SIV or HIV strains. However, the conclusory statements in the Robinson Declaration (Paper No. 15), which was mainly relied upon by Appellants for the enablement of the full breadth of the claimed invention, stating that "consistent with failure to achieve long-term reductions in viral loads, all of the vaccine animals exhibited steadily declining CD4+ cells", that "the trial was terminated at one year post-challenge", that "at this time, the three macaques in the gene-gun only group, and one of the two control macaques (the one with the steady CD4+ level), had succumbed to AIDS (figure 8), and that "the second control monkey and the four monkeys in the multiple route group did not have clinical signs of AIDS at the time of euthanasia", not only do not show any reasonable enablement for the claimed invention on the basis of the Wands factors, but also lend further evidentiary support as to the well-established difficulty in the art of SIV or HIV vaccines

in developing vaccines that produce sufficient specific CTL responses and subsequent immunoprotective effect against any clinical symptom arisen as a result of a SIV or HIV infection in a vaccinated host. Note also that the time for progression of a clinical symptom as a result of an SIV or HIV infection in a real world infectious mammal is much longer than a year, and as such, the evidentiary support showing that only the four macaques in the multiple group did not have clinical signs of AIDS one year post challenge with the laboratory SIVmac251 clone that harbors the same antigen encoded by the immunized DNA plasmids cannot be reasonably extrapolated to any immunoprotective response in primates or humans at risk of being naturally infected by any wild typed SIV or HIV strain.

Furthermore, although the Pardoll and Beckereig references provide some indication of the state of the art in 1995, they in no way provider any clear and convincing evidence that DNA vaccine against SIV or HIV infection, using any route of administration of any type of DNA construct including non-naked DNA vaccines, ~~is~~ was routine and reasonably predictive at the time the invention was made. In fact, Wang (DNA and Cell Biology, Vol. 12, No. 9, 1993; IDS, also cited by Pardoll and Beckereig) teaches that even though an induction of general immune response against HIV antigens *env, tat* and *rev* expressed from the injection through skeletal muscles of a DNA plasmid construct has been shown in an experimental murine model, which is not an art-recognized model for a real world utility in the art of SIV or HIV vaccine, in the specific case of HIV, where antigenic diversity of the envelope protein is a problem for vaccine

design, further investigation of strategies is necessary (page 803, column 2).

Note also that the resulting data obtained from the SIVmac251 model, as disclosed in the Robinson Declaration, in which at the one year post-challenge when the trial was terminated, the three macaques in the gene-gun only group, and one of the two control macaques (the one with the steady CD4+ level), had succumbed to AIDS (figure 8), is further indicia of the lack of reasonable predictability of the claimed DNA SIV or HIV vaccine methods by using any route of administration of any DNA transcription unit encoding any SIV or HIV antigen, even though gene gun administration of naked DNA has been well-established in the prior art for producing an immune response against an encoded antigen by the naked DNA. Furthermore, the fact that a few DNA vaccines that are not even relevant to SIV or HIV DNA vaccines have been developed since the filing of Appellant's application, certainly does not by itself rebut the examiner's assertion regarding undue experimentation on the basis of the Wands factors in an analysis of Appellant's invention as broadly claimed. In fact, the examiner's position and the doubts expressed by the art of record are further reiterated in Robert Cooke (Health & Discovery, page B27, October 3, 1995, Nassau and Suffolk Edition, submitted previously by Appellants), which quoted doubtful statements from a skilled artisan, David Weiner, a molecular immunologist at the University of Pennsylvania Medical University:

> "Our chimpanzee work suggests that DNA vaccines [naked DNA vaccines] are likely to be useful in humans, but not necessarily against HIV", and
> " it is not a panacea that is going to change everything".

Moreover, the fact that a DNA construct has been developed and shown to confer an increase of detectable immune response in some animal models is not the issue. The issue is that the scientific community has had and is having difficulty developing generally successful SIV or HIV (AIDS) virus DNA vaccines, and that the art is not even today as predictable as Appellant has suggested that it was back in 1992-1/1994. Appellants do not explain with clear and convincing evidence why the assessment of the field by skilled artisans of record is wrong as it applies to DNA vaccines for providing a protective effect in vaccinated host that is at risk of being infected by any SIV or HIV virus strain. Even if Appellant's disclosed plasmids encoding specifically named SIV antigens were shown to generate a protective effect in the SIV model by the multiple route of administration, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation for those skill in the art to experiment with DNA immunization so as to provide any immunoprotective effect against SIV or HIV infection in a vaccinated mammal in the context of

the real-world utility as intended by the as-filed application at the time the invention was made.

Animal Model

In addition and with respect to Appellant 's belief that the SIVmac251 macaque model is an art-recognized model being accepted by the skilled artisan at the time the invention was made (1993-1/1994) as being predictive not only for SIV infection in primates but also for HIV infection in humans (pages 7-8 of the reply brief), Appellants had relied on the Gardner (1991, page 268) and McClure (1990, page 287) references in order to support the Appellant's position.

Response:

A simple indication that the SIV model is useful for studying of vaccine candidates for SIV/HIV by the Gardner and McClure back in 1990 and 1991 prior to the filing date of the as-filed application does not lend any credible evidence that demonstrates that at the time the invention was made, notwithstanding the specifically named obstacles raised by the scientific community at the time the invention was made and even now, the SIV model is an **art-recognized model or standardized model** for a skilled artisan to reasonably conclude that the claimed invention would have provided any and/or all immunoprotective response in any mammal against any naturally occurring infection by any SIV or HIV strain, particularly in view of the reasons set forth in the immediately preceding paragraphs. Contrary to Appellant's assertion, even Gardner (1991, Antiviral Research, 15, 1991, 267-286) states:

"Question remaining to be answered in both SIV and FIV models are:

(1) the duration of immunity,
(2) the extent of protection against heterologous strains and mucosal infection,
(3) protection against infection with cell-associated virus and
(4) the role, if any, of cellular immunity in vaccine protection/
Initial attempts at post-infection immunotherapy with SIV vaccines have not yet been successful" (page 267).

In fact and more specifically as to the doubts as to the lack of reasonable correlation between the use of an SIV model for studying the pathogenesis of AIDS and the use of an SIV model as art-recognized model for AIDS DNA vaccine, Johnson (Intern. Rev. Immunol. Vol. 8, 1992, pp. 55-63) states:

"A very notable difference between SIV and HIV is variation in the V3 cystein loop in gp120. In HIV-1, this loop is the principal neutralizing domain in the Env protein and is highly variable from isolate to isolate, perhaps indicating immune selection. In contrast, the SIV "V3 loop" homologue is highly conserved across all isolates of SIVmac/sm. Furthermore, sequential clones taken from animals inoculated with SIV derived from cloned DNA also demonstrate a lack of variation in this region of gp120 [29, 30, 42]. Because of the intense interest in the SIV model as a vaccine development tool for HIV-1, this observation clearly has important implications. If the envelope structures of SIV and HIV-1 differ in a significant way regarding elicitation of protective immune responses after immunization (or infection), then conclusions regarding vaccine trials with SIV in macaques may not be directly applicable to HIV-1 vaccine development. It will be important to resolve this question so that data from SIV vaccine studies can be properly interpreted with respect to HIV-1" (page 59 through page 60).

Even in April 1994, 3 months after the filing date of the as-filed application, Gilboa and Smith (TIG April 1994, Vol. 10, No. 4, pp. 139-144) states:

"The drawbacks to using SIV model to assess HIV gene therapy approaches include...the differences in the biology of SIV and HIV" (page 140 through page 141); and

"In summary, the *in vitro* and *in vivo* model systems currently available for assessing the efficacy and safety of gene therapy approaches to HIV infection have considerable

limitations, and conclusions drawn from these systems must be tempered by their questionable predictive value" (page 142, column 1).

Even in the Lu *et al.* reference (June 1996, J. Virology, Vol. 70, No. 6, 1996, pp. 3978-3991, cited by Appellants), which discloses and discusses the SIV model by using multiple route of administration of the very same plasmid DNA as shown in the Robinson Declaration, Lu *et al.* indicates that while the four monkeys receiving DNA by three routes did not develop opportunistic infection (AIDS) prior to the termination of the trial (1 year) as the three monkey in the gene gun-only group did, this difference in survival did not correlate with differences in antibody and CTL responses, which responses are well-recognized within the scientific community as being crucial for a successful vaccination effect against a SIV or HIV infection, did not correlate with differences in levels of postchallenge infection, or did not correlate with differences in the rates of CD4- cell decline (page 3998, column 2). In fact, Lu *et al.* suggests that the difference in survival could have been due to *chance* (page 3998, column 2). Such statements or conclusions, as also expressed by the totality of the art of record as a whole, do provide substantially convincing evidence for the lack of reasonable predictability of the claimed invention and the lack of reasonable correlation between the use of an SIV model for studying the pathogenesis of AIDS and the use of an SIV model as art-recognized model for AIDS DNA vaccine.

Based on the findings above-that all of the Wands factors other than the level of skill in

the art weigh in favor of nonenablement: It is the examiner's position that the specification does not provide adequate guidance to enable practice of the claimed invention without undue experimentation. Rather, as in a recent Federal Circuit case, the "teachings set forth in the specification provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment practicing a DNA vaccine encoding *env* or *pol* SIV antigen an SIV model so as to further study the physiological activity of a challenged SIV and to plan for future work on the making of a putative DNA vaccine that would overcome the obstacles that were expressed in the art of record...; they do not provide sufficient guidance or specificity as to how to execute that plan." In re Wright, (CA FC) 27 USPQ2d 1510 (1993), Enzo Biochem Inc. v. Calgene Inc., 188F .3d 1362, 1374, 52 USPW2d 1129, 1138 (Fed. Cir. 1999). See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a genetic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable of the public to understand and carry out the invention.").

In addition and as analogously explained in In re Wright, (CA FC) 27 USPQ2d 1510 (1993), the appealed claims are directed to methods of using DNA vaccines in a mammal (primates or humans) at risk of being infected by an SIV or HIV infection, which must by definition trigger an immunoprotective response in the host vaccinated; mere antigenic response or reduction of viral load at 4 weeks or 6 weeks post-challenge is not enough. In addition, Appellants attempt to claim in many of the appealed claims *any and all* DNA vaccines encoding

any SIV or HIV antigen, which must elicit immunoprotective activity in any mammal toward any SIV or HIV virus. In fact, in Wright's case, the court decision states:

> "[M]many of the appealed claims encompass vaccines against AIDS viruses and that, because of the high degree of genetic, antigenic variations in such viruses, no one has yet [even in 1993 when the court decision was made], years after his invention, developed a generally successful AIDS virus vaccine" (page 1513);

Furthermore and as analogous to the court decision in *In re Wright,* the general description and the single example in the Robinson Declaration, directed to a uniquely tailored macaques model under a laboratory environment of generating a reduction of viral load of a laboratory SIVmac251 clone that harbors the same antigen encoded by the immunized DNA plasmid, did nothing more in 1992-1/1994 than invite experimentation to determine whether other SIV or HIV DNA vaccines having *in vivo* immunoprotective activity against any real world or wild type strain of SIV or HIV that infects primates or humans could be constructed for other SIV or HIV viruses (see page 1514 of the Wright's case). Like the court's analysis and conclusion in the Wright's case, Appellants in this as-filed application have failed to establish by evidence or substantially convincing arguments, that in 1992-1/1994 (the claimed priority date through the filing date of this as-filed application), a skilled scientist would have believed reasonably that Appellant's showing of a reduction of viral loads within a statistically insignificant 6 weeks post challenge with a particular laboratory strain of SIV virus could be extrapolated with a reasonable expectation of success to other SIV viruses, let alone HIV viruses,

and/or an immunoprotective effect against any SIV or HIV virus. Note that the art of record even as late as 1998, clearly indicates that the genetic diversity existing among HIV viruses alone required further experimentation or testing for an efficacy of any a real world protection in an inoculated mammal, and that this efficacy becomes apparent only because of observations of increased survival of the inoculated mammals that begin to manifest AIDS symptoms relative to those that are not vaccinated. Appellants have failed to point out with any particularity that the as-filed specification coupled with the scientific literature existing during 1992-1994, as a whole, reasonably or substantially supports Appellant's claimed invention. Consequently, Appellants have failed to provide the examiner with any justification for finding that the Examiner erred in maintaining the Examiner's position, even with respect to methods of using specifically named and exemplified plasmid DNA by multiple routes of administration that includes at least a gene gun administration so as to provide a partial protection in a mammal infected by any SIV virus.

For the foregoing reasons, it is the examiner's position that the evidence as shown in the Robinson Declaration coupled with Appellant's disclosure and the state of the prior art, may support the patentability of an invention different from that of an immunization method of providing any immunoprotective response in any mammal at risk of being infected with a real world SIV or HIV strain, *e.g.,* methods of reducing viral loads by using Appellant's exemplified plasmids DNA by using a multiple routes of administration that includes at least a gene gun delivery; but they do not support the patentability of the appealed claims when these claims are

given the scope that Appellants state that they intend them to have. Appellants have not shown with any substantially convincing evidence for pointing out how the enablement requirement is satisfied as to the each of the claims independently. On this basis, the examiner respectfully submits that the examiner's position should be sustained.

Respectfully submitted,

George C. Elliott, Ph.D.
Supervisory Patent Examiner
Technology Center 1600
CONFEREE

DAVE T. NGUYEN
PRIMARY EXAMINER

DTN
Feb. 28, 2002

DEBORAH J. REYNOLDS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
CONFEREE

Patricia Granahan
Hamilton, Brook, Smith & Reynolds
Two Militia Drive
Lexington MA 02173